# Surveillance of Childhood Cancer: Trends, Clusters and Other Concerns

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RESEARCH • TREATMENT PREVENTION • EDUCATION

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# Goals

- What is a cluster?
- Some examples of clusters
- How often do clusters occur?
- Why is it important to study clusters?
- How do we respond to clusters?
- What are some ways of improving response:
  - In terms of epidemiologic goals?
  - In terms of addressing community concerns?
- A preliminary assessment
- *(I omit a discussion of why clusters occur due to time constraints, but would be willing to do so later)*

# What is a cluster

- “two or more cases occurring close together”
- “5 cases representing at least a 5-fold increase in risk…seen by a single physician over a short period of time”
- “occurrence of a greater than expected number of cases within a small geographic area and/or within a short period of time (i.e., 3-5 years)”

# Cases DO Cluster!  Some Examples

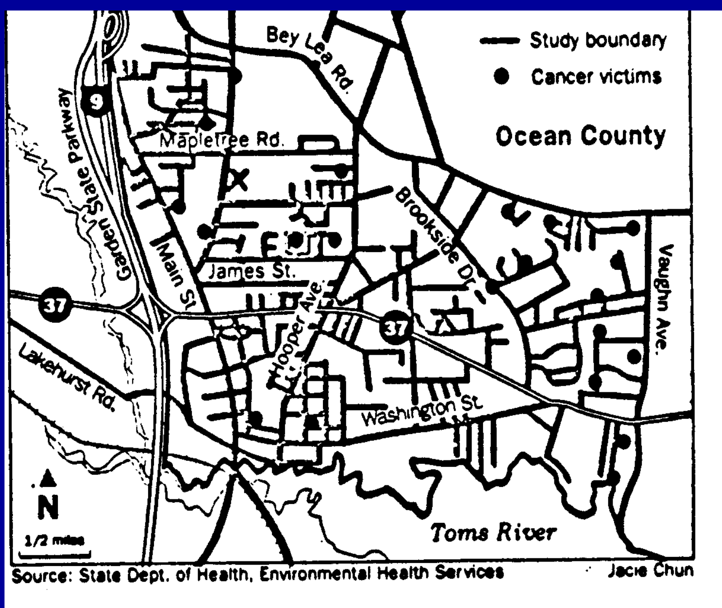
- Childhood Leukemia  (several dozen studies since the 1950s)
- Minimata Disease (1950s)
- **Thalidomide and phocomelia (1960s)**
- DES and vaginal cancer (1971)
- Lymphoma (1970s)
- BSME and lung cancer (1973)
- **Vinyl chloride monomer and liver cancer (1974)**
- Legionnaires Disease and pneumonia (1976)
- **DBCP and male infertility (1977)**
- Kepone and neurotoxicity, infertility (1978)
- HIV/AIDS (1981)
- Leukemia on Meadow St., CT (emfs--1980s)
- Leukemia near Seascale Nuclear Facility (1980s)
- Cancer in NY Giants football players (1987)

# A Typical Community Cluster Report

- A few to several dozen reported cases
- Cases aggregated, e.g., in space, time…
- No known exposures
- No population at risk delineation
- Limited demographic information
- No residence history information
- No surveillance data available

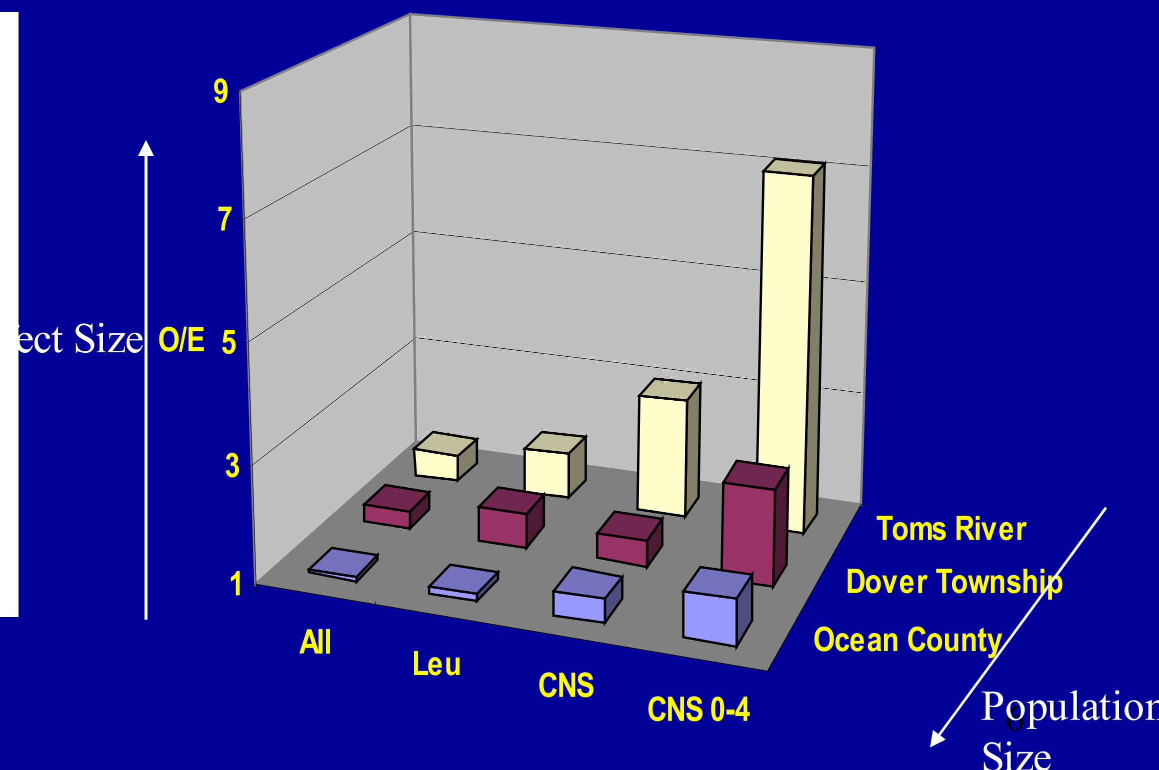
# Toms River, NJ: Reported CNS Cluster

- 1995-1996 Concern about cancer excess raised by nurse at CHOP
- Associations of prenatal exposure with female childhood leukemia with:
  - Drinking water, proximity to effluent pipeline, industrial air contaminants




From Asbury Park Press

**Childhood Cancer Rates 1979-1991**



# Another Cluster: Fallon, NV

- Large excess (RR~35)
  - Summer 2000—5 cases of childhood ALL
  - By end of 2001, 15 diagnosed
  - 0.2 per year expected (population 8,300)
- Home of Navy's "Top Gun" Training
- Ideas Under Investigation
  - Airborne jet fuel release; jet fuel pipeline leaks
  - Population mixing hypothesis (50,000 transients/year)
  - Arsenic in drinking water
- Tungsten

# An Overview of Cancer Cluster Reports in US

- 1,100 to 1,650 per year
    - (Aldrich et al. 1991; Greenberg and Wartenberg 1991; Trumbo 2000)
  - Childhood leukemia is most frequent
  - Major come directly from the public
  - Reports likely biased (not data-based)
- Typical response is reactive
  - Few, if any, result in etiologic association
  - Huge drain of resources for health departments
  - Often result in much animosity from community
- Are there more effective response strategies?
  - Active surveillance???

# Why Do I Believe It Is Important to Study Clusters?

IT IS GOOD PUBLIC HEALTH PRACTICE

- Public concern—***A Local Disease Excess***
  - Clarify of misconceptions—Allay unfounded concerns
  - Initiate study when concerns are well founded
- Encourage Remediation—***Disease Prevention***
  - Determine if situation is a sentinel of a larger problem
  - Identify unknown exposure situations
- Facilitate Scientific Discovery—***Etiology***
  - Identify new exposure-disease link
  - Identify new carcinogens

# When Should We Investigate?

- Situation—among the worst
  - Region has “unusual” incidence
  - Pattern is persistent
  - Possible source of risk identified

# When have we investigated clusters?

- Situation generates attention and pressure
  - Persistent residents
  - Media coverage
  - Political pressure

***Is it surprising that many clusters do not provide convincing etiologic data?***

# Realistic Methodologic Goals

- DATA DRIVEN Approach
  - Identify high exposure/risk situations needing intervention/remediation/education
    - Changes the nature of the epidemiologic question
    - Responsive to public concerns
  - For example, prioritize for epidemiologic follow up
    - Focus specific exposure-disease hypotheses
    - Identify regions most likely to yield useful and interpretable results from further study
    - Target data collection efforts
  - *"The payoff from clustering research comes from the specific hypotheses that emerge to explain the observed pattern of excess occurrence."* --- Rothman (1990)

# Controversy over *Active* Cluster Surveillance

- Against
  - Will identify many situations requiring investigation
  - Will not result in etiologic associations
  - Will be large drain on health department resources
- In Favor
  - Will identify very few situations requiring investigation
  - Will focus on most serious (unusual) situations rather than current, highly-biased “community report” approach
    - Could require presence of risk factor to trigger investigation
  - Will increase likelihood of finding etiologic association
  - By being proactive, could improve community relations
- The Controversial Issue
  - ***How many childhood cancer clusters identified through surveillance would require in depth investigation?***

# What Issues Would *Active* Surveillance Address?

- General Question:
  - ***Where and in Whom Do Childhood Cancers Occur?***

    ***Do the cases form any clusters?***
- Scientific Issue:
  - ***What are the major risk factors for childhood cancer?***

    ***Are cluster(s) associated with environmental risks?***
- Policy Consideration:
  - ***Would routine assessment for childhood cancer clusters be meaningful scientifically and helpful for community communication/collaboration?***

***Should we consider Active Surveillance?***

# Some Previous Empirical Results

- Reynolds et al. 1996 *(childhood leukemia: 134 cases)*
  - Examined 4 county (101 community) area
  - Data fit Poisson distribution (1 area in excess, as predicted)
- Alexander et al. 1998 (*childhood leukemia: 13,351 cases)*
  - Examined 16 EU Countries and Australia
  - Found slight excess ($\beta$ =1.7% extra Poisson variation)
- Belluc et al. 2006 *(childhood acute leukemia: 4,897 cases)*
  - Examined all acute childhood leukemias in France, 1990-2000
  - Overall found slight excess ($\beta$ =0.5%, p=0.23)
  - In most densely populated area 1990-1994 ($\beta$ =5.5%, p=0.01)
- McNally et al. 2006 *(childhood cancer: 32,295 cases)*
  - Examined all childhood cancers in UK, 1969-1993, ages 0-14
  - *Clustering for ALL (p=0.04; S=1.3%), for ALL ages 0-4 (p=0.03)*
- Summary: Statistically Significant Clusters are RARE

# An Empirical Study: The Distribution of Childhood Cancer in Washington State 1990-2001

- Demographics
  - Age, race, gender, cancer type
- Socioeconomics
  - Income, poverty
- Statistical Distribution
  - Overall Randomness (Poisson assumption)
  - Clustering (local: SaTScan, global: MEETS,…)

***This project is "A Work in Progress"***

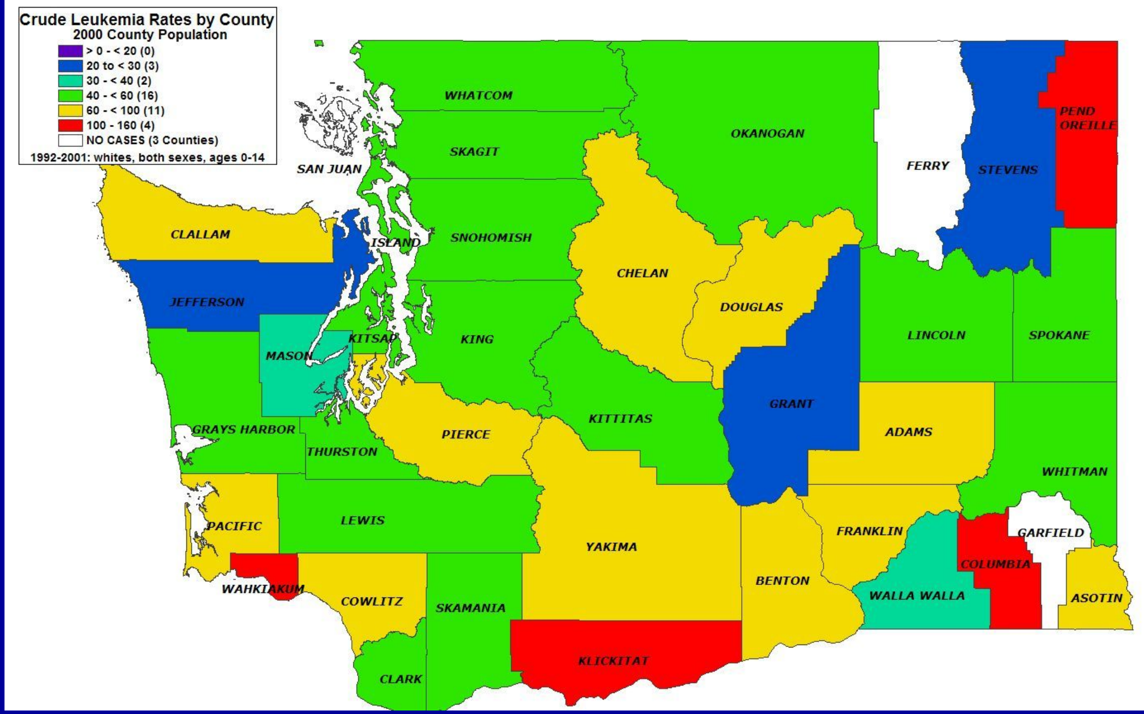
# Number of Childhood Cancers

| Cancer Type | Number |
|---|---|
| All Cancers | ٢,٨٩٢ |
| Leukemias | ٦٧٨ |
| Acute Lymphocytic | ٥١٣ |
| Central Nervous System | ٥٥٥ |
| Lymphomas | ٤٢٠ |
| Hodgkins Disease | ٢٣٧ |
| Non-Hodgkins | ١١٥ |
| Carcinomas/Maligant Epithelial | ٣٦٧ |
| Soft Tissue Sarcoma | ٢٢٢ |
| Germ Cell | ١٦٨ |
| Sympathetic Nervous System | ١٥٨ |
| Malignant Bone Tumors | ١١٢ |
| Renal Tumors | ١٠٢ |

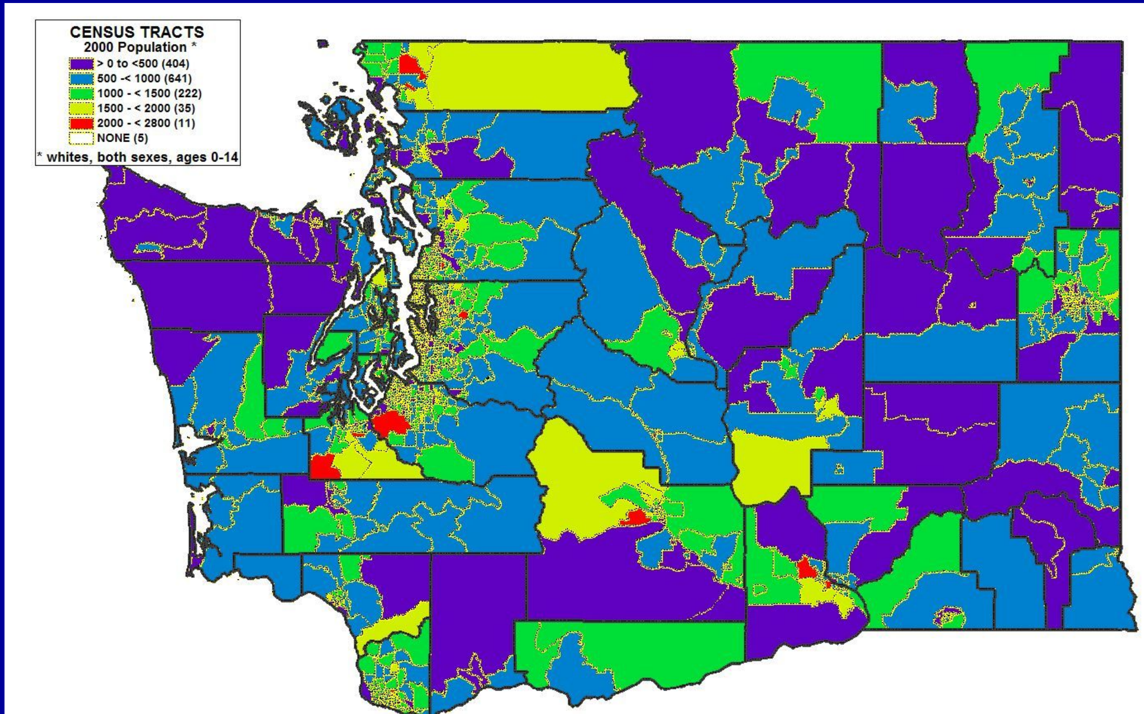
# Cancer Cases by Demographics

| Age Group | Males | | Females | | Total |
|---|---|---|---|---|---|
| | White | Non-White | White | Non-White | |
| 0 – 4 | 396 (44.9%) | 56 (6.3%) | 367 (41.6%) | 64 (7.5%) | 883 |
| 5 – 9 | 233 (47.8%) | 36 (7.4%) | 193 (39.6%) | 26 (5.3%) | 488 |
| 10 – 14 | 243 (43.8%) | 31 (5.6%) | 252 (45.4%) | 29 (5.2%) | 555 |
| 15 – 19 | 419 (43.4%) | 41 (4.2%) | 432 (44.7%) | 74 (7.7%) | 966 |
| TOTAL | 1291 | 165 | 1244 | 193 | 2892 |

Childhood Leukemia in Washington State 1992-2001




Childhood Population in Washington State 2000



# What would happen if we looked at cancer patterns on a regular basis and asked the following:

- Do the data follow a Poisson distribution?
  - Poisson goodness of fit test
  - Potthoff-Whittenhill test
- Are the data spatially autocorrelated?
  - Moran's I
  - Geary's c
- Do the data cluster?
  - Local: SaTScan (Kulldorff)
  - Global: MEETS (Tango)
  - Other Tests

# Washington State Results
## *(conducted at county level)*

- Poisson Distribution Assessment
  - CNS $p<0.97$
  - Leukemia $p<0.87$
    - ALL $p<0.94$
  - Lymphoma $p<0.53$
- Potthoff-Whittinghill
  - None statistically significant
  - Tract level analysis is in process
    - Expect some significant
    - issue is size of overdispersion

- Spatial Autocorrelation
  - None statistical significant
- CNS I=-0.004 c=0.92
- Leuk I=-0.061 c=0.97
  - ALL I=-0.007 c=0.89
- Lym I=-0.052 c=0.96

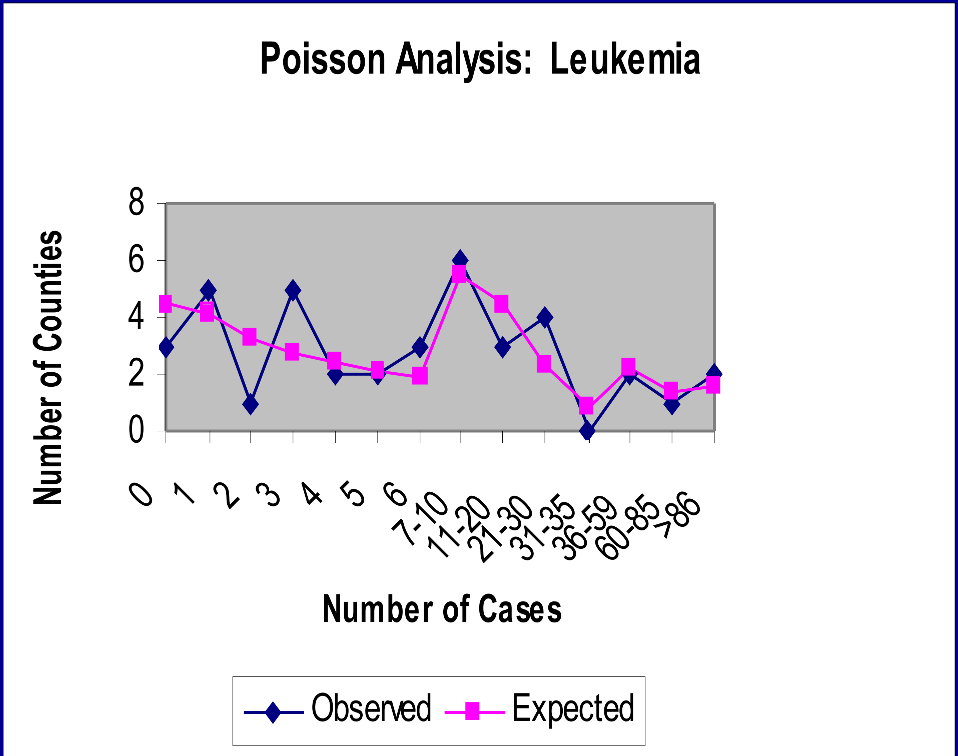
- Exp(I)=-1/n Exp(c)=1.0

# Poisson Plots

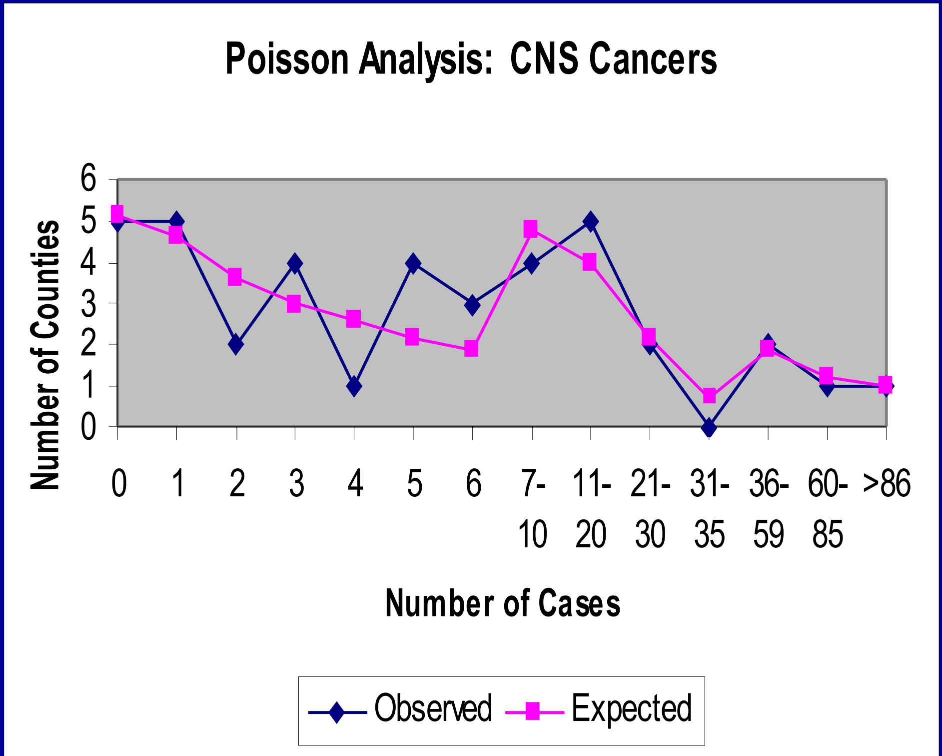
## *(conducted at county level)*

Number of Counties With
Observed/Expected Number of Cases

All Leukemias ($p<0.87$)




CNS Cancers ($p<0.97$)



# SaTScan Results

## *(conducted at census tract level)*

### Spatial Clusters

| Cancer | Cases | Expected | Relative Risk | p-value |
|---|---|---|---|---|
| | | | | |
| CNS | 4 | 0.21 | 19.596 | 0.227 |
| Hepatic | 2 | 0.04 | 48.185 | 0.192 |
| Leukemia | | | | |
| *CML* | *3* | *0.13* | *28.678* | *0.036* |
| Lymphocytic | 6 | 18.93 | 0.309 | 0.739 |
| Non-lympocytic | 2 | 0.02 | 122.104 | 0.100 |
| TOTAL | 5 | 0.55 | 9.129 | 0.676 |
| Lymphoma | | | | |
| Burkitts | 6 | 1.09 | 6.173 | 0.273 |
| Hodgkins | 3 | 0.11 | 28.537 | 0.262 |
| Non-Hodgkins | 2 | 0.02 | 95.963 | 0.141 |
| TOTAL | 3 | 0.19 | 15.829 | 0.883 |
| Renal | 5 | 0.43 | 12.395 | 0.064 |
| Retino | 16 | 5.75 | 3.447 | 0.085 |
| Soft Tissue Sarcoma | 4 | 0.33 | 12.427 | 0.454 |

### Space-Time Clusters

| Cancer | Cases | Expected | Relative Risk | p-value |
|---|---|---|---|---|
| | | | | |
| CNS | 110 | 71.08 | 1.684 | 0.261 |
| Hepatic | 3 | 0.07 | 45.595 | 0.150 |
| Leukemia | | | | |
| CML | 2 | 0.00 | 466.052 | 0.012 |
| Lymphocytic | 20 | 6.01 | 3.421 | 0.352 |
| Non-lympocytic | 2 | 0.02 | 1218.840 | 0.024 |
| TOTAL | 25 | 8.35 | 3.071 | 0.291 |
| Lymphoma | | | | |
| Burkitts | 2 | 0.01 | 183.113 | 0.182 |
| Hodgkins | 3 | 0.05 | 66.071 | 0.351 |
| Non-Hodgkins | 3 | 0.03 | 100.434 | 0.065 |
| TOTAL | 10 | 32.27 | 0.293 | 0.178 |
| Renal | 4 | 0.07 | 59.053 | 0.015 |
| Retino | 6 | 0.43 | 15.313 | 0.039 |
| Soft Tissue Sarcoma | 8 | 0.74 | 11.228 | 0.061 |

Yellow Font signifies p≤0.05

Also note the number of cases in each "cluster"

*(Need to do some subanalyses, consider multiple comparisons)*

# Summary

- Understanding the spatial pattern of childhood cancers may help us:
  - Better understand etiology
  - Identify true excesses
    - Possibly leading to prevention/intervention
  - Communicate more effectively with the public
- Research Needs
  - Continue to assess historical data for better understanding of typical patterns and aberrations
  - Develop protocols and decision rules for analyses that are:
    - Sensitive to detecting local excesses (true positives)
    - Have few mistakes (false positives, false negatives)
    - Understandable to practitioners
- Conclusion
  - Based on preliminary analyses, *Active Surveillance* looks feasible scientifically and potentially advantageous for communities

# What is the Focus of the Controversy?

- Are clusters caused by environmental contamination?
- Given the history of investigations, is it worthwhile to study clusters:
  - In view of
    - the cost
    - the science
    - the politics
    - in terms of public health

- ***It depends on who you are and your goals***

# Why Do Clusters Occur?

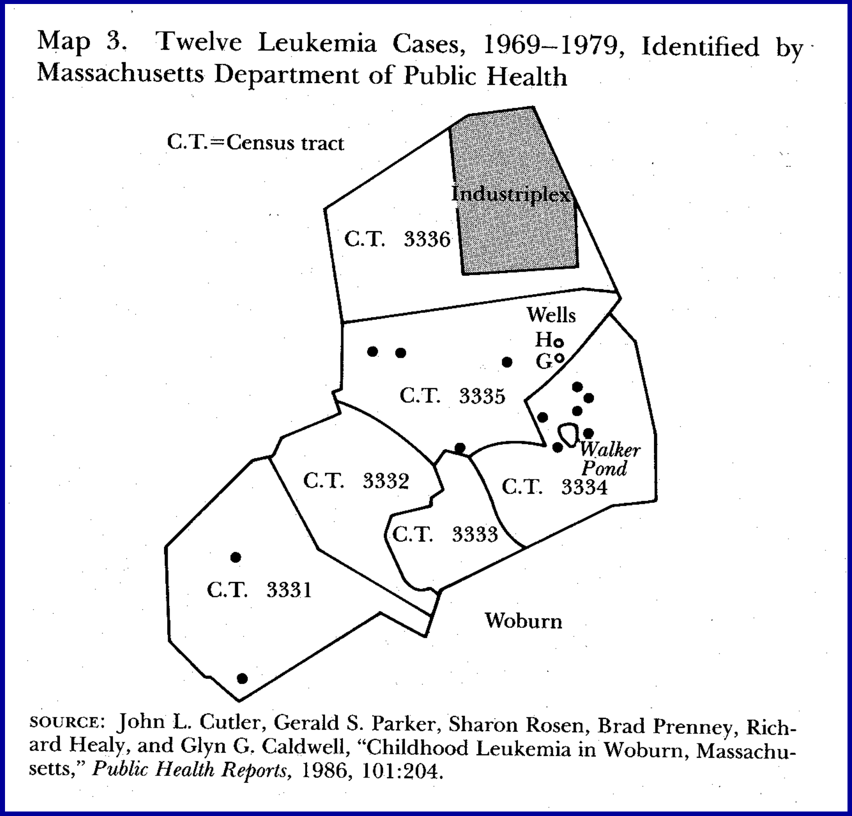
- Common demographics (age, race, genetic)
  - genetic examples emerging (breast cancer)
- Common interpersonal contact (biological)
  - several validated examples (Legionella, HIV)
- Common exposures (chemical)
  - workplace:  several examples (VC, DBCP)
  - pharmaceuticals:  few examples (DES, thalidomide)
  - environment:  controversial
- Common behavior (e.g., smoking, drinking)

# *Known or suspected risk factors associated with childhood cancers*

- **Radiation**
  - **Ionizing**—unlikely except possibly near Hanford
  - **Non-ionizing** (power lines)—possible; data not easily available
- **Air Pollution** (traffic)—data inconclusive
- **Diet/Nutrition**—some associations
- **Genetics**—some syndromes; other alterations strongly suggestive (esp. B-cell ALL)
- **Chemicals**
  - **Solvents** (benzene)—*data from NATA—mainly AML in adults*
  - **Pesticides**—some positive studies
  - **Parental Occupation**—several positive associations
- **Infection** (Population mixing)—controversial

- abcdefghijklmnopqrstuvwxyz
- ABCDEGHIJKLMNOPQRSTUVWXYZ

# Woburn, MA: *"A Civil Action"*




- State Study (Parker and Rosen 1981)
  - 12 childhood cancers observed, 5.3 expected, $p$=0.008
- Harvard study positive (1984)—controversial
  - 12 childhood leukemia cases where 5.3 expected
- New cases found after wells closed
  - MADPH study finds ***prenatal water exposure*** a risk (1996)

From DiPerna